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26. (Amended) The DNA sequence of claim 16 [15] wherein said protein is human tissue plasminogen activator or hepatitis B surface antigen.

Please cancel claims 4, 14 and 20.

REMARKS

The Remarks section includes the following sections:

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I Summary of the Response to rejections under 35 USC § 112 ¶ 1

This summary is merely to orient the reader, Applicant's arguments are provided in full text below.

Written Description

The invention in the instant application is a combination of three art-known elements. It is a vector which includes: a region which includes a milk protein promoter, a signal sequence, and a nucleic acid encoding a protein other than the protein normally associated with the milk protein promoter, (sometimes referred to herein as a heterologous gene or protein).

A written description inquiry must be made from the standpoint of one having the skill and knowledge of the art. The greater the level of skill and knowledge the less specificity of disclosure is needed, and that information well known in the art need not be described in detail. The knowledge and skill and knowledge of the art with regard to the small genus (about 7 members) of milk promoters and then to the skill in the art, especially with regard to the manipulation of promoters or sequences which include such promoters was considerable.

The genus of milk protein promoters was well characterized and defined in the art at the time of filing. This is shown by the five references (all published prior to the filing date of the instant application) discussed below. These references provide the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant amount of DNA sequence for the promoter regions, of each of five of the seven types of milk promoters. The disclosure of the references is summarized in Table 1 below.

The level of skill in the art, with regard to the manipulation of eukaryotic promoters was well developed. The isolation, recombinant manipulation, and use of mammalian promoters, was routine in the art at the time of filing. By the filing date, it was routine in the art to obtain mammalian promoters and to couple them to heterologous genes. Numerous references which show the level of skill and predictability with regard to eukaryotic promoters are discussed below.

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The identifying characteristic provided by the applicant for a sequence or region which includes a milk specific promoter is the name of the promoter. Given the fact that these promoter regions were already known in the art, that is sufficient--it is sufficient in that it clearly conveys what was invented--the "essential goal" of the written description requirement. To point to the promoter by naming, when the promoter is structurally and physically characterized in the art, says "use this specific structurally characterized art-known element." The degree of detail needed to convey the realization that the inventor was in possession depends on the essential character of the invention and the level of skill and knowledge in the art. If the art was devoid of information as to milk specific genes and promoters a great level of detail would of course be called for. However, in this case the level of knowledge and skill in the art is considerable and namely of the known element is sufficient.

The Guidelines state that more evidence is required in emerging or unpredictable technologies. Biology is a technology in which some endeavors are predictable and some are unpredictable. Situations in which only function is recited may not satisfy the written description requirement. In particular, where new genes are claimed a mere recitation of name or function is insufficient. Neither is the case in the instant matter. Structural information, including sequence information, on the milk promoters was known in the art. The claims in the instant matter, unlike those in Amgen, Fiers, and U.C. v. Lilly, are not drawn to novel gene sequence defined only by function in the specification and not known in the art. The essential characteristics of the invention in Amgen, Fiers, and U.C. v. Lilly was the determination of a nucleotide sequence not in the art.

Amgen and its progeny stand for the proposition that, absent structural information, the claiming of a gene, by mere function, does not satisfy the written description requirement. The structure of a gene is not implicit in simply stating the name of the gene or stating the desired function, e.g., EPO activity. The instant facts are significantly different. The specification does not merely recite a desired function - which here might be - the production of a heterologous protein (in milk) - but names

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elements of known structure and function, by naming there elements it provides, implicitly, sufficient structure to satisfy the written description requirement.

With regard to the genus of "milk promoters" the specification explicitly describes two types, WAP and α-lactalbumin. Given the level of skill and knowledge in the art, including the fact that the promoters were in the art, and that methods for using and testing promoters were in the art or enabled by the specification, two of seven is sufficient to satisfy the requirement. In the case of milk promoters a member of five of the seven species was known in the art—a remarkably well-characterized genus. The Guidelines provide that "what constitutes a "representative number" is an inverse function of the skill and knowledge of the art." Given this level of knowledge in the art one would only need one or a few examples to demonstrate the scope of the claim, to demonstrate possession of an invention that can use any of those species in the milk promoter genus.

The specification directs the use of caseins as well. Their relevance is described by the use of that term. Three of the four caseins were well defined in the art.

In summary, given the level of skill and knowledge in the art, particularly extensive structural knowledge of the promoter regions, the disclosure provides an adequate written description of the invention.

Enablement

The genus of milk protein promoters was extremely well characterized and defined in the art at the time of filing. This is shown by the five references (all published prior to the filing date of the instant application) discussed below.

These references provide the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant amount of DNA sequence for the promoter regions of each of five of the seven types of milk promoters. The disclosure of the references is summarized in Table 1,

The isolation recombinant manipulation, and use of mammalian promoters, and notably cell and tissue-specific promoters, was routine in the art at the time of filing. By the filing date,

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it was routine in the art to obtain mammalian promoters and to couple them to heterologous genes. A non-exhaustive list of references which report such work is discussed below, following the discussion of milk promoters. In one example, Ciliberto et al. (1985) Cell 41:531-540, a promoter was obtained and used to regulate a heterologous gene. The vast majority of nucleotide sequence of the promoter region was not disclosed (only 133 of 1200 basepairs of sequence was disclosed in Ciliberto et al.). Thus, the sequence of the region was not needed to enable the construction or use of the promoter. Most if not all of the significant steps in the isolation of mammalian promoters followed by Ciliberto et al. had already been executed for the milk promoters at the time of filing (see the milk promoter references discussed above). Therefore, to use a milk promoter, one would not have to isolate and characterize a promoter from scratch as was done in, e.g., Ciliberto et al. One would not even need to perform all of the steps of the art-known method disclosed in Ciliberto et al.

Given the extent to which milk protein promoters were described in the art, and the level of predictability of isolating mammalian promoters, one of ordinary skill would be able to isolate a representative spectrum of milk protein promoters from genomic DNA.

The examiner's position appears to be that because most of the references which characterized milk promoters did not actually point to a particular fragment, narrow down the exact sequences needed for activity (it is pointed out that independent claim 16 is explicitly limited to a region which includes a promoter), and test it for activity, the promoters are not enabled. As is discussed above, the genus of milk protein promoters was well characterized and defined in the art at the time of filing.

The specification at least provides guidance choosing specific promoter containing regions. This guidance would allow one of ordinary skill in the art to choose a size fragment. It only remains to follow the remaining steps, which the examiner admits are enabled.

In demanding that the art actually point to a specific sequences functional fragment or sequence data, the examiner asks for far too much. First the sequence data is not needed (even though the references in the art do provide it), second the law allows for considerable experimentation. The examiner argues that the disclosure is an invitation to invent. The level of

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skill in the art, e.g., Ciliberto et al, which disclosed the isolation and use of a eukaryotic promoter as well as the other references sited above, suggest that the examiner has incorrectly assessed the state of the art and the abilities of one of ordinary skill.

The examiner is demanding that each element of a specific embodiment of the invention be present in the art, identified, and proved ready for immediate use, with essentially no modification, in the invention. This is not the law. The law allows some, even, considerable experimentation. Given the art's ability to manipulate eukaryotic promoters, even tissue specific promoters, the level of experimentation required to practice is not undue.

II. The Office Action

The claims have been rejected under 35 USC §101, and 35 USC §112, first paragraph.

III. 35 U.S.C. § 101

The claims have been provisionally rejected under 35 U.S.C. § 101 for obviousness-type double patenting over claims of 08/927,936 and 08/246,259.

The provisional double patenting rejection will be addressed when claims are found allowable.

IV. 35 U.S.C. § 112, ¶ 1

Claims 1, 2, 5-9, 11, and 16-29 have been rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the invention was filed, had possession of the claimed invention".

The rejection of claims 1, 2, 5-9, 11, 16-19 and 21-29 are respectfully traversed. Claim 20 has been cancelled.

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A. Analysis under the written description Guidelines

The written description rejection is analyzed below in view of the Patent and Trademark Office's written description "Guidelines".[1] The Guidelines provide that: the examiner has the initial burden of overcoming a strong presumption that the written description, as filed, is adequate; that a written description rejection should be rare; and that the analysis for written description is to be made on a case-by-case basis. We turn now to the analytical procedure set out in the Guidelines.

1. Analysis of the claims

The Guidelines begin (Guidelines II.A.1) by requiring a careful analysis of the claims. The examiner is instructed to determine if sufficient structures, acts, or functions are recited to make the scope and meaning of the claim clear. The section ends with the provision that:

> The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 USC sec. 112, paragraph 1, for lack of adequate written description.

2. Determination of the essential feature of the invention

The Guidelines go on to require that the examiner "Review the entire application to understand what applicant has described as the essential features of the invention" see, the Guidelines, II.A.2. The Guidelines require:

> The examiner is to determine the correspondence between what applicant has described as the essential identifying characteristic features of the invention, i.e., what the applicant has demonstrated possession of, and what applicant has claimed. (II.A.2.)

The invention in the instant application is a combination of three art-known elements. It is a vector which includes: a region which includes a milk protein promoter,

[1] The Revised Interim Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, Paragraph 1 "Written Description" Requirement published in the Federal Register, Vol. 64, No. 244, December 21, 1999, at pages 71427-71440, referred to herein as the "Guidelines."

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a signal sequence, and a nucleic acid encoding a protein other than the protein normally associated with the milk protein promoter, (sometimes referred to herein as a heterologous gene or protein). Milk promoter regions were known in the art. Structure, including restriction analysis, nucleotide sequence data, and location of specific structures was known for a broad spectrum of milk promoters. The essence of the invention, i.e., the essential identifying characteristic feature of the invention, is the combination of these several art-known elements in a new way, namely the functional coupling of milk protein promoter with a signal sequence and a heterologous protein encoding nucleic acid, in a vector. The essential identifying characteristics are, first and foremost, the idea of combining the elements. Clearly that concept of combining is explicitly set out in the claims and throughout the specification. The applicant is also in possession of the prior art elements which are to be combined. As is discussed below, each of the elements to be combined was known, separately, in the art. By naming and pointing to these well-known elements, the applicant has demonstrated possession of them for the use in the invention—combining them into a vector.

It is important to understand what the invention is and what it is not. The invention is not the discovery of a new genetic sequence, as was, e.g., the invention in Amgen v. Chugai, 927 F.2d 1200 (Fed.Cir. 1991), Fiers v. Revel, 984 F.2d 1164 (Fed.Cir. 1993), and U.C. v. Lilly, 119 F.3d 1559 (Fed.Cir. 1997). The essential identifying characteristic is not the claiming of a novel gene. Had the inventor pursued a different invention and goal then that might have been the case. But it is not, the inventor is not attempting to claim a novel gene or even a novel promoter, but rather a combination of known elements sufficiently described for the purposes of the claim, by the specification.

a. Written description analysis requires a determination of the level of skill and knowledge in the art

The Guidelines require that review must be conducted from the standpoint of one skilled in the art at the time the application was filed. (And this of course means the analysis will be different in the case where the claimed material is unknown in the art as opposed to where the claimed material is a combination of known elements.) In

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conjunction with this requirement that the inquiry be made in light of the art, the Guidelines require that information which is well known in the art does not have to be discussed in detail:

> Such a review is conducted from the standpoint of one of skilled in the art at the time the application was filed, and should include a determination of the field of the invention and the level of **skill and knowledge** in the art. Generally there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art does not have to be described in detail in the specification. (the Guidelines II.A.2, footnotes omitted, emphasis added)

Bearing in mind that the inquiry must be made from the standpoint of one having the skill and knowledge of the art, that the greater the level of skill and knowledge the less specificity of disclosure is needed, and that information well known in the art need not be described in detail, we turn first to the knowledge and skill of the art with regard to the small genus (about 7 members) of milk promoters and then to the skill in the art, especially with regard to the manipulation of promoters or sequences which include such promoters. Applicant specifically points out that it is not making an enablement-based argument for the satisfaction of the written description requirement (as was made by Fiers in Fiers v. Revel) but is conducting the review of the level of skill and knowledge required for a written description analysis, as mandated by the Guidelines.

i. **The level of skill and knowledge in the art with regard to sequences which include a milk promoter**

The genus of milk protein promoters was well characterized and defined in the art at the time of filing. This is shown by the five references (all published prior to the filing date of the instant application) discussed below.

These references provide the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant

amount of DNA sequence for the promoter regions, of each of five of the seven types of milk promoters. The disclosure of the references is summarized in Table 1.

(1) Table 1. Summary of Milk Promoter Information in Art at the Time of Filing

	Milk Serum Proteins			Caseins			
	α-lact-albumin[1]	β-lactoglobin	Whey Acid Protein[2] (WAP)	α-casein[3]	β-casein[4]	γ-casein[5]	κ-casein
5' flanking regions cloned in the art?	Yes, 8.5 kb	-	Yes, 9 kb	Yes, 7.1 kb	Yes, 14.6 kb	Yes, 9 kb	-
Restriction Analysis provided in the art?	Yes	-	Yes	Yes	Yes	Yes	-
3' end of regulatory region determined in the art?	Yes	-	Yes	Yes	Yes	Yes	-
Promoter region nucleotide sequence data provided in the art?	1,247 bps	-	1,175 bps	680 bps	780 bps	90 bps[4]; 680 bps[3]	-
5' structures, e.g., TATA or CAAT boxes, upstream regulatory binding sites identified?	Yes	-	Yes	Yes	Yes	Yes	-

1. Qasaba and Safaya (1984), *supra.*
2. Campbell *et al.* (1984), *supra.*
3. Yu-Lee *et al.* (1986), *supra.*
4. Jones *et al.*, (1985), *supra.*
5. Yu-Lee and Rosen (1983), *supra.*

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(2) Individual milk promoters described in the art

(α) **α-lactalbumin**

Qasba and Safaya (1984) *Nature*308:377-380 (submitted herewith as Exhibit A) discloses the nucleic acid sequence of the rat α-lactalbumin gene and identifies promoter region structures. The authors isolated several λ clones which span the rat α-lactalbumin gene. One clone contains at least 8.5 kb of isolated 5' flanking promoter sequence. The reference provides restriction analysis of the region (*Ibid*, Fig. 1, Methods). The reference further provides the nucleotide sequence of 1247 nucleotides of the 5' flanking region (*Ibid*, Fig.1). The 3' end point of this region was defined by primer extension and S1 nuclease mapping of the mRNA. "The 5' end of the rat α-LA mRNA was located at G, position 1,247, by the primer extension method." The authors identify the signature TATA box and promoter elements for progesterone receptor binding.

(b) **Whey Acid Protein (WAP)**

Campbell *et al.* (1984) *Nucl. Acids Res* 12:8685-8697 (submitted herewith as Exhibit B) describes the structure of rat and murine WAP promoters. The authors isolated genomic DNA spanning the rat WAP gene. The reference provides a restriction map of the region (*Ibid*, Fig. 1). With regard to the promoter region, the reference provides that at least 9 kb of the isolated DNA is 5' flanking sequence of the WAP gene. The authors defined the 5' flanking region relative the mRNA start site from the cDNA sequence. The sequence of 1175 base pairs of promoter is provided in Fig. 3. The authors identified a TATA box, a CAAT box, glucocorticoid response elements, and a progesterone response element within the promoter. For example, "A competitive DNA cellulose binding assay has identified multiple glucocorticoid receptor binding sites between 566 and --1250 in the rat WAP gene... (*Ibid*, p. 8695)."

The authors also isolated genomic DNA spanning the mouse WAP gene. A restriction map is provided for this DNA. Approximately 2.6 kb of 5' flanking sequence were described. The sequence of 325 base pairs of the promoter was provided. The TATA box and a progesterone receptor binding site were identified.

The rat 5' WAP regulatory sequences are contained in a 12.6 kb partial EcoRI-HhaI fragment. The regulatory sequences closest to the mRNA start site reside on a 2.0 kb EcoRI-HhaI fragment.

(c) α-casein

Yu-Lee *et al.* (1986) *Nucleic Acids Res.* 14:1883-1902 (submitted herewith as Exhibit C) describes the structures of the promoter region of rat α-casein and bovine α-casein promoters and compares theses structures with those of rat β-casein and rat γ-casein promoters. The reference provides a restriction map of the 11.5kb rat α-casein locus (*Ibid*, Fig. 2A). With regard to the promoter region, the reference provides that, "The λα1 clone contains approximately 7.1 kb of 5' flanking DNA..." The 3' end of the 5' regulatory region was determined by comparison to previously published cDNA sequence, primer extension, and S1 nuclease digestion results (see Hobbs and Rosen (1982) *Nucleic Acids Res.* 10:8079-8098). The nucleic acid sequence of 680 basepairs of the 5' flanking DNA was disclosed. The signature TATA box was located.

In addition, the authors isolated λ clones spanning the rat γ-casein gene and the bovine α_{s1}-casein gene. The sequence of 680 basepairs of both these promoters was provided. The authors identify conserved blocks of homology between the rat α-casein promoter, rat β-casein rat promoter, γ-casein promoter, and bovine α_{s1}-casein promoter (e.g., Table 1B).
Stewart *et al.* (1984) *Nucleic Acids Res.* 12:3895-3907 (submitted herewith as Exhibit D) report the nucleotide sequence for bovine α-casein and identify the promoter region structures. The reference provides the sequence of 35 nucleotides of the promoter region and indicates the location of the TATA box.

The rat α-casein 5' regulatory sequences are shown to be contained in a 5.4 kb partial EcoRI-NdeI fragment.

(d) β-casein

Jones *et al.* (1985) *J Biol Chem* 260:7042-7050 (submitted herewith as Exhibit E) report the complete genomic region of the rat β-casein gene including promoter-associated regions. The reference describes 34.4 kb of isolated genomic DNA spanning the rat β-casein locus. The

reference provides a restriction map of the entire locus (*Ibid*, Fig. 1 of Supplement, p. 7049). With regard to the promoter region, the reference provides that, "In addition to the 7.2 kb β-casein gene, these clones contain 14.6 kb of 5' flanking DNA. (*Ibid*, p. 7042)." The promoter was further defined relative to the mRNA start site by the cDNA 5' end sequence. The nucleic acid sequence of 780 bp of 5' flanking sequence is provided. The signature promoter elements, TATA box and CAAT box, were within the sequenced region, as were hormone response elements for glucocorticoids and progesterone. As noted above, Yu-Lee *et al.* (1986) also characterized the β-casein promoter and compared it to the bovine α-casein, rat α–casein, and rat γ-casein promoters.

(c) <u>γ-casein</u>

Yu-Lee and Rosen (1983) *J Biol Chem* 258:10794-10804 (submitted herewith as Exhibit F) provide the rat γ-casein gene including promoter region structures. The reference describes 35 kb of isolated genomic DNA spanning the rat γ-casein locus. With regard to the promoter region, the reference provides that, "Approximately 9kb of 5' flanking sequences are found in the λγ9 and λγ10 clones...(p. 10796, col. 1, par 3)." The reference provides a well characterized restriction map of the region (*Ibid*, Fig. 2). The authors defined this 9 kb region as 5' flanking sequence relative to the 5' end of the mRNA. The 5' end of the mRNA was located by fine restriction mapping of the genomic sequence relative to cDNA probes. Not only was the promoter region characterized by restriction mapping but, the sequence of 90 basepairs of the promoter was provided. Furthermore, the reference located two typical eukaryotic promoter sequences, a noncanonical TATA box at –29 to –23, and a CAAAT box at –86 to –80. As noted above, Yu-Lee *et al.* (1986) disclosed 680 basepairs of the rat γ-casein promoter, and compared it to the bovine α-casein, rat α–casein, and rat β-casein promoters.

The rat γ-casein 5' regulatory sequences are contained in a 7.7 kb partial EcoRI fragment.

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ii. **The level of skill and knowledge in the art with regard to the manipulation and use of eukaryotic promoters**

(1) Overview

We turn now to the level of skill in the art, particularly with regard to the manipulation of eukaryotic promoters. The isolation, recombinant manipulation, and use of mammalian promoters, and notably cell and tissue-specific promoters, was routine in the art at the time of filing. By the filing date, it was routine in the art to obtain mammalian promoters and to couple them to heterologous genes. Given the disclosure in the milk promoter references, it would be routine for one skilled in the art to pick a region and combine it with the other elements required by the claims.

A non-exhaustive list of references which report such work is discussed below. In one example, Ciliberto *et al.* (1985) *Cell* 41:531-540, a promoter containing region was obtained and used to regulate a heterologous gene. The vast majority of nucleotide sequence of the promoter region was not taught by the reference (only 133 of 1200 basepairs of sequence was disclosed in Ciliberto *et al.*). Thus, the entire sequence of the region was not needed to enable the construction or use of the promoter.

Most if not all of the significant steps in the isolation of mammalian promoters followed by Ciliberto *et al.* had already been executed for the milk promoters at the time of filing (see the milk promoter references discussed above). Therefore, to use a milk promoter, one would not have to isolate and characterize a promoter from scratch as was done in, e.g., Ciliberto *et al.* One would not even need to perform all of the steps of the art-known method disclosed in Ciliberto *et al.*

Approximately two years prior to the filing of the application, Campbell *et al.* (1984, *supra*) noted the presence of "105 eukaryotic 5' flanking sequences in GenBank™ (*Ibid*, p. 8694)." By the filing date, it was routine in the art to obtain mammalian promoters and to couple them to heterologous genes, as is discussed in the following examples.

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(2) Examples

(a) Ciliberto *et al.* (1985) *Cell* 41:531-540

Ciliberto *et al.* submitted herewith as Exhibit G) obtained genomic nucleic acids, determined the 3' end of the 5' regulatory region, isolated a promoter-containing fragment, and coupled it to a heterologous sequence. In particular, the authors isolated λ clones spanning the human α1-antitrypsin locus, mapped the transcription initiation site by primer extension, and S1 nuclease digestion, and thereby defined the α1-antitrypsin promoter as the region immediately 5' to the mRNA start site. The authors fused a heterologous CAT gene to 1200 base pairs of 5' flanking sequence, and found that the resulting construct not only had promoter activity, but the promoter activity was cell-type specific. Fig. 11 (*Ibid*) illustrates that this promoter fusion construct was active in Hep3B cells but not HeLa cells.

Notably, these results in at least Ciliberto *et al.* were obtained without the vast majority of nucleotide sequence of the promoter region (only 133 of 1200 basepairs of sequence was disclosed). Thus, the sequence of the region was not needed to enable the construction. Note that most if not all of the significant steps in the isolation of mammalian promoters followed by Ciliberto *et al.* had already been executed for milk promoters at the time of filing (see the milk promoter references discussed above). Therefore, to use a milk promoter, one would not have to isolate and characterize a promoter from scratch as was done in e.g., Ciliberto *et al.*

(b) Walker *et al.* (1983) *Nature* 306:557-561

Walker *et al.* (submitted herewith as Exhibit H) demonstrated that a heterologous gene fused to the promoter containing region of the insulin and chymotrypsin gene is expressed only in specific cells, i.e. those that express the endogenous gene. With regard to the promoters, the reference provides that:

> DNA sequences containing the 5'-flanking regions of the insulin and chymotrypsin genes were linked to the coding sequence of the chloramphenicol acetyltransferase (CAT) gene. The insulin gene recombinant elicits preferential expression of CAT activity when introduced into cells producing insulin; similarly the chymotrypsin gene recombinant elicits preferential expression in chymotrypsin-producing cells.

(c) Krumlauf *et al.* (1985) *Mol Cell Bio* 5:1639-1648

Krumlauf *et al.* (submitted herewith as Exhibit I) demonstrated *in vivo* promoter activity for isolated 14 kb 5' flanking DNA of the mouse α-fetoprotein. The isolation of this regulatory region was previously described in Ingram *et al.*.(1981) *Proc Natl Acad Sci USA* 78:4694-4698. This region and a smaller 7kb region were cloned upstream of a minigene which serves a reporter for promoter activity. The resulting constructs were microinjected mice. The authors "conclude that the modified genes, which included either 7 or 14 kilobase pairs of 5' flanking DNA, contained the DNA sequence information to direct both tissue-specific expression and developmental regulation."

(d) Ott *et al.* (1984) *EMBO J* 3:2505-2510

Ott *et al.* (submitted herewith as Exhibit J) demonstrated that a heterologous gene fused to the promoter containing region of the rat albumin gene is expressed only in specific cells, i.e., those that express the endogenous gene. From a plasmid subclone of this region, the authors "constructed a transient expression vector containing 400 bp of rat albumin gene immediate 5'-flanking sequences inserted 5' to the bacterial enzyme chloramphenicol acetyl transferase (CAT). ... The albumin flanking sequences are able to direct highly efficient CAT expression, compared with the control vectors, only in cells which express their own albumin gene..." (The isolation of the rat albumin regulatory region was previously described in Sargent *et al.* (1981) *J. Mol. Cell. Biol.* 1:871-883.)

(e) Ornitz *et al.* (1985) *Nature*313:600-602

Ornitz *et al.* (submitted herewith as Exhibit K) "demonstrate that a fusion gene containing only 213 base pairs of [rat] elastase I gene sequence directs expression of hGH [a reporter] in pancreatic acinar cells." Transgenic mice were generated with the fusion gene and remarkably the hGH reporter was not expressed in any of the tissues tested, except the pancreas, the tissue wherein the endogenous elastase I gene is expressed. The isolation of the rat elastase I

promoter DNA was previously reported in Swift *et al.* (1984) *Cell* 1984 38:639-646 and Sargent *et al.* (1979) *Proc Natl Acad Sci USA* 76:3256-3260.

(f) Palmiter *et al.* (1982) *Nature*300:611-615

Palmiter *et al.* (submitted herewith as Exhibit L) coupled a region which included the mouse metallothionein-I gene promoter to nucleic acid encoding the rat growth hormone. Mice microinjected with this DNA construct expressed the rat growth hormone gene in liver indicating that the promoter was functional *in vivo*. In addition, Palmiter and Brinster in US 4,579,821 describe a plasmid which "include[s] a DNA sequence coding for herpes simplex virus thymidine kinase which is operatively associated with the promoter/regulator DNA sequence of the mouse metallothionein-I gene." The isolation of the promoter of the mouse metallothionein-I gene promoter by methods similar to those described below was described in Durnam *et al.* (1980) *Proc Natl Acad Sci USA* 77:6511-6515.

(g) Magram *et al.* (1985) *Nature*313:338-340

Magram *et al.* (submitted herewith as Exhibit M) demonstrated that the "5' portion of the mouse β^{dmaj} adult globin gene and 1.2 kilobases (kb) of 5' flanking DNA, joined to the 3' portion of the human β-globin gene..." was sufficient to function as a cell specific promoter. The authors "conclude that the mouse/human hybrid β-globin gene in three different transgenic mouse lines is inactive in embryonic blood cells, and is first expressed in the fetal liver erythroblasts. This pattern of switching is identical to that of the endogenous adult β-globin genes... ." The isolation of genomic DNA spanning the mouse β-globin gene had been previously reported.

(h) Ishii *et al.* (1985) *Proc Natl Acad Sci USA* 82:4920-4924

Ishii *et al.* (submitted herewith as Exhibit N) isolated more than 10 kb of genomic DNA in λ clones spanning the human EGF-receptor locus using degenerate oligonucleotides. Further they have "localized the EGF receptor gene 'promoter' in cloned human genomic DNA (*Ibid*, p. 4923)." The promoter was defined relative to the mRNA start site as determined by primer

extension and S1 nuclease mapping. The nucleotide sequence of 460 base pairs of the promoter were provided. The authors demonstrated that the promoter was functional in an *in vitro* transcription assay.

(i) **Melton *et al.* (1984) *Proc Natl Acad Sci USA* 81:2147-2151**

Melton *et al.* (submitted herewith as Exhibit O) isolated 60 kb of genomic DNA spanning the mouse HPRT gene, of this, greater than 10 kb was 5' flanking sequence. The authors demonstrated that the first 850 basepairs of 5' flanking sequence is a functional promoter in a construct containing a cDNA fusion.

(j) **Reynolds *et al.*** (1984) *Cell*38:275-285

Reynolds *et al.* (submitted herewith as Exhibit P) used a clone walking technique to isolate more than 30 kb of DNA spanning the hamster HMG CoA reductase locus, of which approximately 1 kb was 5' flanking sequence. The promoter was defined by the 5' end of the mRNA, determined by primer extension and S1 nuclease protection. About 300 nucleotides of the promoter was sequenced. The promoter was fused to the CAT gene and showed activity in transfected cells.

(k) **Valerio *et al.* (1985) *EMBO J* 4:437-443**

Valerio *et al.* (submitted herewith as Exhibit Q) isolated 66 kb as cosmid clones spanning the human adenosine deaminase gene, approximately 10 kb of this region is 5' flanking sequence. The 3' boundary of the promoter was defined by S1 nuclease and primer extension experiments. The authors demonstrated that 135 base pairs of the 5' flanking sequence when fused to a cDNA was an active promoter in cultured cells. The sequence of the region was provided.

3. Determination of whether the applicant was in possession of the claimed invention

The next step in the Guidelines requires a determination of:

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Whether There is Sufficient Written Description To Inform a Skilled Artisan That Applicant Was in Possession of the Claimed Invention as a Whole at the Time the Application Was Filed (the Guidelines, II.A.3.)

The Guidelines make no a priori rules as to how possession can be shown in fact, the Guidelines provide the opposite by stating explicitly that "Possession may be shown in a number of ways." (II.A.2.a.) The Guidelines provide that possession can be shown by (a) actual reduction to practice, (b) reduction to drawings, or (c):

> ...by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, [39] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[40] What is conventional or well known to one skilled in the art need not be disclosed in detail.[41] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[42] (emphasis added)

Applicant points out the lack of rigid a priori rules about what constitutes satisfaction of the requirement and an emphasis on factual analysis. The approach is the opposite of an automatic application of prior fact specific holdings to very different inventions.

(a) In view of the state of the art, naming the art-known promoters is sufficient to describe them

As discussed above, the genus of milk protein promoters was well characterized and defined in the art at the time of filing. This is shown by the five references (all published prior to the filing date of the instant application) discussed below.

These references provide the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant

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amount of DNA sequence for the promoter regions, of each of five of the seven types of milk promoters. The disclosure of the references is summarized in Table 1. In addition, as is discussed in section IV.A.2.a.ii, page 14 above, the manipulation of sequences which include a promoter region was known and routine in the art.

The identifying characteristic provided by the applicant for a sequence or region which includes a milk specific promoter is the name of the promoter. Given the fact that these promoter regions were known in the art, that is sufficient--it is sufficient in that it clearly conveys what was invented--the "essential goal" of the written description requirement. To point to the promoter by naming it, when, as here, the art is replete with structural and functional characterization of the promoter, says "use this specific structurally characterized art-known element." The degree of detail needed to convey the realization that the inventor was in possession depends on the essential character of the invention and the level of skill and knowledge in the art. If the art was devoid of information as to milk specific genes and promoters a great level of detail would of course be called for. However, in this case the level of knowledge and skill in the art is considerable and naming the known element is sufficient.

The knowledge of milk protein promoters, including partial sequence information, was well developed in the art. In the light of this knowledge, the essential nature of the invention, and the level of skill in the art, recitation of the promoter demonstrates possession. Once the inventor teaches one to combine the elements, very little, indeed no more than identifying the element, is needed to demonstrate possession.

The Guidelines explicitly recognize the level of description needed depends on how much was known in the art about the subject matter. The Guidelines recognize and:

> ...distinguish between novel and old elements in a claim to clarify that the amount of written support needed in an application can vary depending on the general knowledge that was readily available in a particular art. (See PTO's response to comments in the Guidelines)

Section II.A.3.a.(1) (c) (ii) of the Guidelines discusses what will satisfy the written description requirement "if the application does not disclose the complete structure of the claimed invention." The examiner is instructed to:

> ...determine whether the specification discloses other relevant identifying characteristics sufficient to describe the claimed invention in such full clear, concise, and exact terms that a skilled artisan was in possession of the claimed invention. (footnotes omitted)

The Guidelines explicitly require that printed publications should be relied on to determine the level of knowledge and skill in the art. With regard to this point the examiner is directed to the section above which shows that printed publications described the promoters including sequence data.

(b) Amgen, Fiers and U.C. v. Lilly do not require a complete sequence in the instant matter.

The Guidelines state that more evidence is required in emerging or unpredictable technologies. Biology is a technology in which some endeavors are predictable and some are unpredictable. Situations in which only function is recited may not satisfy the written description requirement. In particular, where new genes are claimed a mere recitation of name or function is insufficient. Neither is the case in the instant matter. Structural information, including sequence information, on the milk promoters was known in the art. The claims in the instant matter, unlike those in Amgen, Fiers, and U.C. v. Lilly, are not drawn to novel gene sequence defined only by function in the specification and not known in the art. The essential characteristics of the invention in Amgen, Fiers, and U.C. v. Lilly was the determination of a nucleotide sequence not in the art.

(i) Amgen

In Amgen, the Court considered what was needed for conception for a claim directed to a gene. The claims at issue in Amgen were directed to a purified and isolated DNA sequence. The court focused on knowledge of the nucleotide sequence in terms of determining whether conception had occurred. For at least some claims considered in

Amgen, see, e.g., claim 2, the functionally defined gene was the only limitation, in a setting where the essential character of the invention was the determination of a nucleotide sequence of a previously uncharacterized gene. There was nothing else one could look to know if the inventor was in possession of the invention and to be able to distinguish the invention from other materials. In contrast, in the instant invention, knowledge of the elements of the claim were in the art. In Amgen, the court stated explicitly that "The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin... "927 F. 2d at 1206. That the court was specifically discussing a novel gene in was shown in Fiers v Revel, where the Court characterized its decision in Amgen as one" in which we addressed the requirements necessary to establish conception of a purified DNA sequence coding for a specific protein".

The invention in Amgen, a new gene sequence, and the instant invention, a vector which includes art known elements, are both, in a physical sense, made of nucleic acid, but otherwise they are quite different. Detailed base-by-base sequence was clearly needed in the case of Amgen, where that was the invention, it was what was new over the art, and, most important here, it was needed to distinguish other materials. In the Amgen invention, knowledge of base-by-base sequence was the invention, in the instant case it is irrelevant.

Nothing in the Amgen holding says that a sequence (let alone a complete sequence) is required to meet the written description in every invention which relates to a nucleic acid. Indeed, the holding was explicitly limited to genes:

> We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated. Amgen at 1206 (emphasis added)

The court relied on structure, in that instance, the knowledge of sequence to distinguish the claimed gene from other genes:

> Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define. Amgen at 1206

The DNA sequence, particularly the entire sequence, of the individual elements of the claimed combination are simply not needed to distinguish the claimed invention from other materials.

Applicant is not arguing that the Amgen Court limited its decision to the exact facts of the case. The decision did appear though to limit it to a claim to a gene. Even if this is not the case, it is beyond argument that the court in Amgen did not require a complete DNA sequence in every claim which recites a composition which includes a nucleic acid.

Amgen and its progeny stand for the proposition that, absent structural information, the claiming of a gene, by mere function, does not satisfy the written description requirement. The structure of a gene is not implicit in simply stating the name of the gene or stating the desired function, e.g., EPO activity. The instant facts are significantly different. The specification does not merely recite a desired function - which here might be - the production of a heterologous protein (in milk) - but names elements of known structure and function, by naming there elements it provides, implicitly, sufficient structure to satisfy the requirement.

(ii) Fiers

In Fiers v. Revel, 984 F. 2d 1164 (Fed. Cir. 1993), Applicants attempted to establish conception of a novel gene by providing a protocol for isolating the gene but no sequence date.

The Fiers court held:

> A bare reference to a DNA with a statement that it can be obtained by reverse transcription is not a description; it does not indicate that Revel was in possession of the DNA. Revel's argument that correspondence between the language of the count and language in the specification is sufficient to satisfy the written

description requirement is unpersuasive when none of that language particularly describes the DNA.

As we stated in Amgen and reaffirmed above, such a disclosure just represents a wish, or arguably a plan, for obtaining the DNA. If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity. To paraphrase the Board, one cannot describe what one has not conceived. Fiers at 1171

The court further held:

We thus determined that, irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility. Fiers at 1169.

The recitation of the name of the promoter, where the promoter is known and well characterized in the art is far more than the mere recitation on the name of an unsequenced gene.

(iii) U.C. v. Lilly

In U.C. v. Lilly, the Court applied the teachings of Amgen to a claim to novel cDNA's which encode insulin. In this case the specification failed to disclose the sequence in the gene, and as would be expected in claiming a novel gene, the claimed subject matter was not taught in the art. The Court found the written description requirement was not met and said, "The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity." In contrast, the instant situation, the name conveys just that.

Like its predecessors, the need for sequence data in Lilly was in the context of a claim, the essence of which was, the elucidation of a novel nucleic acid sequence. When speaking more broadly, the court was careful to qualify its remarks.

Accordingly, naming a type of material known to exist, in the absence of knowledge as to what the material consist of, is not a description of that material. (emphasis added).

That is a critical distinction, we are not facing the situation which presents an absence of knowledge as to the claim element--it is known in the art. Thus here, having accomplished a great deal more and satisfies the written description requirement.

(iv) Summary of the Case Law

In summary the milk promoter regions were known in the art. The art taught the structure, including sequence data for milk promoter containing regions. See the data summarized in Table 1. This situation is entirely effect from the facts in Amgen, Fiers, and U.C. v. Lilly, where the Applicants claimed novel genes, with nothing other than function.

4. The Specification satisfies the written description requirement for the species claims, i.e., claims 13 and 19.

The Guidelines require that for each claim drawn to a single species the examiner should determine (a) whether an actual reduction to practice is described, (b) if the invention is complete as evidenced by a reduction to drawings, or (c):

> Whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the invention. (Guidelines II.A.3.1)

Each species claimed is now analyzed. Although other species are disclosed in the specification, the only species claims are to α lactalbumin see claims 13 and 19. The detailed description is met by satisfying criteria (c) set out in the Guidelines.

a. Claims 13 and 19

α lactalbumin promoter-containing regions were known in the art. See Qasaba and Safaya and the discussion thereof in section IV.A.2.a.i., pages 16-17 above. The written description for α lactalbumin is provided for by naming the promoter.

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5. **The specification provides a written description of the claimed Genus, claims 1 and 16.**

a. The Genus

We turn now to the genus claims. We first consider the genus of milk promoters. It is important to keep in mind that the genus of milk specific promoters is very small. This doesn't mean that applicant does not need to describe the genus, but that relatively fewer species will describe the genus. It is noted that all the promoters share common canonical status. The genus consists of about seven types of promoters. They are as follows:

Whey acid promoter (WAP);

α - lactalbumin;

B - lactoglobulin;

α - casein;

B - cascin;

K-casein; and

γ-casein.

The genus can be divided into to "sub" genera: the "milk serum proteins" which consists of three proteins (WAP, α-lactalbumin, and B-lactoglobulin); and the "caseins", which consists of four proteins (α, B, K, and gamma casein). As is shown in Table 1, regions which include five of the seven types of milk promoters were known in the art, including partial sequence, at the time of filing. (For the subgenera, promoter-continuing regions for 2 of 3 were known for the milk serum proteins; and promoter-continuing regions for 3 of 4 were known for the caseins.) Thus, these genera were exceedingly well characterized.

As is discussed above, the guidelines provide for several ways in which the written description requirement can be satisfied, by: (a) actual reduction to practice; (b) reduction to drawings; or (c) by a disclosure of relevant identifying characteristics sufficient to show possession of the genus.

We now turn to a description of the promoters provided in the specification.

b. The species described in the specification.

(i) The WAP promoter

Constructs containing the WAP promoter were made and deposited with the ATCC as ATCC No. 67032 and 67033. See page 10 and 12 of the specification.

Figures 1-5 present drawings of a WAP promoter-containing vector of the invention.

The specification identifies the WAP promoter (see, e.g., page 9 of the specification) by that term, which in view of the level of knowledge and skill in the art, see, e.g., Campbell et al. (1984) discussed above, is a description sufficient to show possession.

Thus, for the WAP promoter, the specification satisfies the written description requirement in all three ways set out in the Guidelines.

(ii) The α-lactalbumin promoter

The specification identifies the α lactalbumin promoter (see page 4), by its art recognized name, which in view of the level of knowledge and skill in the art is a description sufficient to show possession. As is discussed herein, Qasba and Safaya et al. (1984) discussed above, provides a detailed characterization of the α lactalbumin promoter.

(iii) The casein promoters

The specification teaches that the casein promoters (see pages 2 and 15) should be used. In view of the level of knowledge and skill in the art, this is a description sufficient to show possession. As is discussed herein, Yu-Lee et al. (1986), Jones et al. (1985) and Yu-Lee and Rosen (1983) provides a detailed characterization of the 3 of the 4 casein promoters.

6. A Representative Number of the Members of the Milk Promoter Genus is described.

The Guidelines provide that the written descriptions requirement for a claimed genus may be satisfied by sufficient description of a representative number of species, by the same standards as discussed for species claims, see, the Guidelines II.3.a.(2). The Guidelines provide as follows:

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> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus.[50] Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.[51]

With regard to the genus of "milk promoters" the specification explicitly describes two specific types, WAP and α-lactalbumin. Given the level of skill and knowledge in the art, including the fact that the promoters were in the art, and that methods for using and testing promoters were in the art or enabled by the specification, two of seven is sufficient to satisfy the requirement. In the case of milk promoters, a member of five of the seven species was known in the art—a remarkably well-characterized genus. The Guidelines provide that "what constitutes a "representative number" is an inverse function of the skill and knowledge of the art." Given this level of knowledge in the art one would only need one or a few examples to demonstrate the scope of the claim, to demonstrate possession of an invention that can use any of those species in the milk promoter genus.

Although individual casein promoters are not expressly named, the specification directs the use of "caseins as well." Their relevance is described by the use of that term. Three of the four caseins were well defined in the art. The applicant did not explicitly name the casein promoters but specified the broad term casein. Although there was no individual naming, this together with the specific naming of the others, helps show one of ordinary skill what is meant he milk promoters and thus put one in possession of the genus. U.C. v. Lilly support the view that there is not just one way to describe a genus.

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In Lilly the Court considered whether the description of a single cDNA species provided a description of two very large genera vertebrate and mammalian. The court held that:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. (emphasis added)

However, the court did not close the door to other methods of meeting the requirement:

> However, it may not be necessary to enumerate a plurality [*28] of species if a genus is sufficiently identified in an application by "other appropriate language." (citations omitted). We will not speculate in what other ways a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin.

We note also that for some milk promoters, namely the WAP and α casein, promoters from more than one species were known. In the case of WAP, rat and murine were known. In the case of α casein rat and bovine were known. We note that all species of a genus need not be described, see the Guidelines, which provide:

> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that genus embraces.[51]

The content of footnote 51 is relevant to this inquiry, as even in the care of a new gene the number of species required is limited. Footnote 51 provides:

> For example, in the genetic arts, it is unnecessary for an applicant to provide enough different species that the disclosure will permit one of skill to determine

the nucleic acid sequence of another species from the application alone. The stochastic nature of gene evolution would make such a predictability nearly impossible. Thus, the Federal Circuit could not have intended that the representative number requires predictability of sequences.

7. **A representative Number of species of the Milk Serum Genus are described.**

Claims 12 and 18 are directed to the sub-genus of milk serum promoters. This sub genus includes three types of promoter. As is discussed above, the WAP and α-lactalbumin species are described. Thus, 2 of the 3 types of milk serum promoters are described.

The examiner has failed to meet the burden, of presenting by a preponderance of evidence why a person skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.

B. Responses to specific remarks made in the Office Action under the Written Description Rejection

On page 6, first full paragraph, of the Office Action the examiner argues that there is nothing in the Guidelines that the holdings in University of California is limited to DNA sequence claims. The court in Lilly held that:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. (emphasis added)

One could certainly argue that a requirement for sequence in U.C. v. Lilly was limited to cDNA or perhaps other gene claims. What is clear is that, perhaps even in the narrow area of cDNA's, and beyond a doubt in other areas, the court did not close the door to other methods of meeting the requirement:

> However, it may not be necessary to enumerate a plurality [*28] of species if a genus is sufficiently identified in an application by 'other appropriate language.'" (citations omitted). We will not speculate in what other ways

> a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin. (emphasis added)

The Guidelines emphasize the case-by-case nature of the inquiry. The examiner is attempting to apply the most narrow holding in the line of cases which follow Amgen to a very different set of claims and a very different invention. In addition, the examiner ignores or gives little weight to the requirements in the guidelines and, in the very cases relied on for the rejection, that the level of knowledge in the art affects the level of disclosure needed.

In the same paragraph the examiner also argues that the physical structure of the promoters is essential and that the art did not teach the structure. First, the physical structure is essential, but the sequence and certainly not the entire sequence, is not essential. The sequence is not claimed. That level of knowledge is simply not needed to describe this invention, as opposed to new gene claims. Second, it should be noted that the art taught structure, including sequence. The examiner argues that there is no physical description of the promoters in the art. This is an incorrect reading of the art. The examiner has not give the nature of the invention and the level of skill and knowledge in the proper consideration and is setting the bar to high for this invention.

V 35 U.S.C. § 112, ¶ 1

Claims 1, 2, 5-9, 11, and 16-29 have been rejected under 35 U.S.C. §112, first paragraph, as not being enabled.

The rejection of claims 1, 2, 5-9, 11, 16-19 and 21-29 are respectfully traversed. Claim 20 has been cancelled.

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The examiner appears to agree that the specification enables the construction of the vector, (see the paragraph which bridges pages 6 and 7 of the rejection), and the making of transgenic animals (see page 11, "The issue is not knowledge of making transgenic non-human mammal. The rejection is the availability of milk protein gene promoters for the breadth of applicant's invention.") As such the discussion here will focus on enablement of milk promoters.

The examiner's position appears to be that because most of the references which characterized milk promoters did not actually point to a particular fragment, narrow down the exact sequences needed for activity (it is pointed out that claim 16 expressly is limited to a region which includes a promoter) and test it for activity, the promoters are not enabled. As is discussed above, the genus of milk protein promoters was well characterized and defined in the art at the time of filing. This is shown by the five references (all published prior to the filing date of the instant application). These references provide the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant amount of DNA sequence for the promoter regions, of each of five of the seven types of milk promoters. The disclosure of the references is summarized in Table 1.

In all five examples, the art provides the genomic region identifies critical 3' end if the regulatory sequence, provides sequence date and identifies structure. It would have been routine for one of ordinary skill to pick a fragment from that disclosed region, especially given the fact that the 3' end is defined by each reference.

See pages 5-6 of the specification which provide:

> A sequence upstream form the transcription start site in the genomic clone constitutes a putative "promoter", a genomic sequence preceding the gene of interest and presumed to be involved in its regulation. The promoter may be isolated by carrying out restriction endonuclease digestions and subcloning steps. Promoters need not be of any particular

length nor to have directly shown any properties of regulation. The mouse WAP promoter was isolated as a 2.6 kb EcoR1-Kpn1 fragment immediately 5' to the WAP signal sequence.

Additional guidance comes from the art. As is discussed in section IV.A.2.a.ii at page ___ above, the art, e.g., Ciliberto et al., Krumlauf et al., Ott et al, and Magram et al., taught the sizes of useful promoter-containing regions. These sizes were, respectively, 1.2 kb, 14 and 7 kb, .4 kb, and 1.2 kb. The specification teaches the use of a 2.6 kb fragment for the WAP promoter. This guidance would allow one of ordinary skill in the art to choose size fragment. It only remains to follow the remaining steps, which the examiner admits are enabled.

In demanding that the art actually point to a specific sequences functional fragment or sequence data, the examiner asks for far too much. First sequence data is not needed to practice the invention, though it is provided in the references. Second the law allows for considerable experimentation. As is shown by the numerous references discussed herein, the art shows that the manipulation of eukaryotic promoters was predictable. The examiner argues that the "mere knowledge of a genomic sequence does not put in the hands of the public the promoter sequence(s)." That may be true, but much more was disclosed here: there was significant discussion of promoter location and provision of sequence and structure for five types of promoter. The examiner argues that the disclosure is an invitation to invent. The level of skill in the art, e.g., Ciliberto et al, which disclosed the isolation and use of a eukaryotic promoter as well as the other references sited above, suggest that the examiner has incorrectly assessed the state of the art and the abilities of one of ordinary skill.

The examiner is demanding that each element of a specific embodiment the invention be present in the art, identified, and proved ready for immediate use, with essentially no modification, in the invention. This is not the law. The law allows some, even, considerable experimentation. Given the art's ability to manipulate eukaryotic promoters, even tissue specific promoters, the level of experimentation required to practice is not undue.

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Contrary to the examiner's assertion, the promoters were available. The art disclosed their location, some of their structural elements including sequence data, taught the manipulation of eukaryotic promoters. Methods of testing are enabled by the specification (e.g., they can be tested in place of the WAP promoter in the WAP transgenic mouse the examiner concedes to be enabled).

VI. 35 U.S.C. § 112, ¶ 2

Claims 1, 2, 5-9, and 111 are rejected under 35 U.S.C. § 112, ¶ 2 as indefinite.

Claim 11 has been amended to meet the rejection.

Claims 1 and 9 are no longer duplicative.

Applicant submits that all of the claims are now in condition for allowance, which action is requested. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 10 Aug 00

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